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Fluid management in sepsis associated acute kidney injury

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ABSTRACT

Sepsis-associated acute kidney injury (SA-AKI) significantly contributes to morbidity and mortality in critically ill patients, necessitating an evidence-based approach to fluid management. Understanding the pathophysiology of SA-AKI and appreciation of the delicate balance between adequate fluid resuscitation and prevention of fluid overload, are essential to deliver optimal management of these patients.

This review highlights the phases of fluid therapy, the strategies for fluid management in SA-AKI, the types of preferred fluids in different phases, and both, pharmacologic and mechanical methods of fluid removal. The application of individualised strategies tailored to specific patient subsets, including those with septic cardiomyopathy or chronic kidney disease remains challenging. A major limitation is that most fluid studies were conducted in critically ill patients in general, rather than patients with SA-AKI. Future research is imperative to study fluid management specifically in SA-AKI, refine therapeutic protocols and guide management to improve patient outcomes.

1. Introduction

Sepsis is one of the most among common aetiologies of acute kidney injury (AKI) in critical care [1]. When sepsis-associated acute kidney injury (SA-AKI) occurs, it significantly increases the risk of morbidity and mortality [2]. Despite advances in critical care, fluid management remains a challenge due to the intricate balance required between timely and adequate fluid resuscitation and the prevention and management of fluid overload [3,4]. Differentiating between *volume responders* and *non-responders* is particularly important (Fig. 1) [5]. As SA-AKI has a complex pathophysiology involving systemic inflammation, hemodynamic instability, and microvascular dysfunction, researchers have highlighted phase-specific approaches to fluid management to optimize patient outcomes. This review examines current evidence and clinical frameworks guiding fluid management throughout the 4 phases of resuscitation from Salvage, Optimisation and Stabilisation to De-resuscitation (Fig. 2) [6]. We also discuss emerging hemodynamic tools for monitoring fluid status, emphasizing the importance of an individualised approach to enhance renal recovery and patient survival [7].

2. Pathophysiology of SA-AKI

Sepsis is the leading cause of AKI in critically ill patients. The pathophysiology of SA-AKI is multi-factorial and includes a complex interplay of systemic and renal-specific inflammation, complement activation, dysregulation of the renin-angiotensin-aldosterone system (RAAS), mitochondrial dysfunction and altered microcirculation [2]. Systemic inflammation is associated with the release of inflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-6, triggering widespread endothelial activation and vascular dysfunction. As a result, the microcirculation is disrupted, leading to heterogenous renal perfusion, capillary leakage, and microvascular thrombosis, ultimately impairing oxygen delivery to tubular cells. Furthermore, dysregulation of the RAAS can worsen renal perfusion, exacerbating ischaemia. Mitochondrial dysfunction leads to impaired cellular energy production and oxidative stress, contributing to further tubular cell injury and apoptosis. Complement system activation during sepsis also promotes leucocyte infiltration and endothelial damage. Sepsis-induced damage of the glycocalyx increases vascular permeability, exacerbating oedema and impairing glomerular filtration. In case of fluid accumulation or cardiac dysfunction, venous congestion aggravates renal hypoperfusion and renal tissue ischaemia [8]. Other contributing factors are the use of nephrotoxic drugs, choice of fluid therapy and comorbidities.

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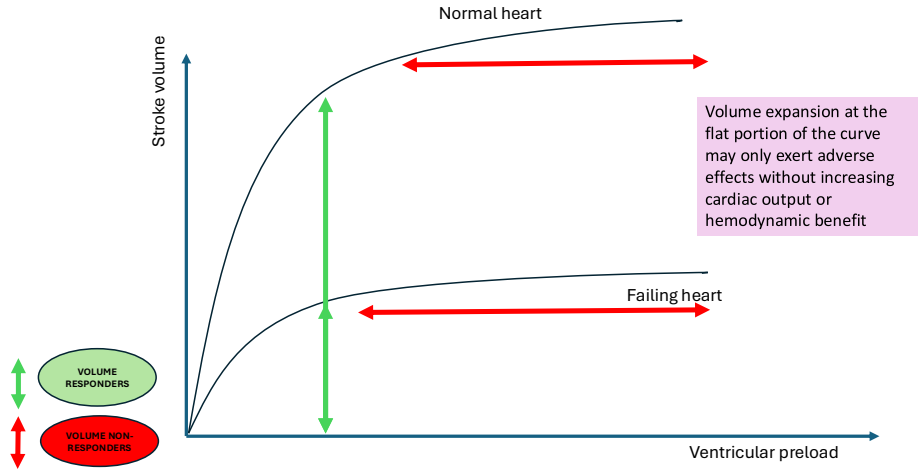
Normal heart
Stroke volume
Volume expansion at the flat portion of the curve may only exert adverse effects without increasing cardiac output or hemodynamic benefit
Failing heart
VOLUME RESPONDERS
VOLUME NON-RESPONDERS
Ventricular preload

Fig. 1. Relationship between volume responders and non-responders in the Frank-Starling curve.
Two curves reflect different heart performance conditions. In the normal heart, ventricular preload increases a significant amount of stroke volume. In contrast, in a failing heart, a significant increase in preload does not increase a substantial amount of stroke volume.

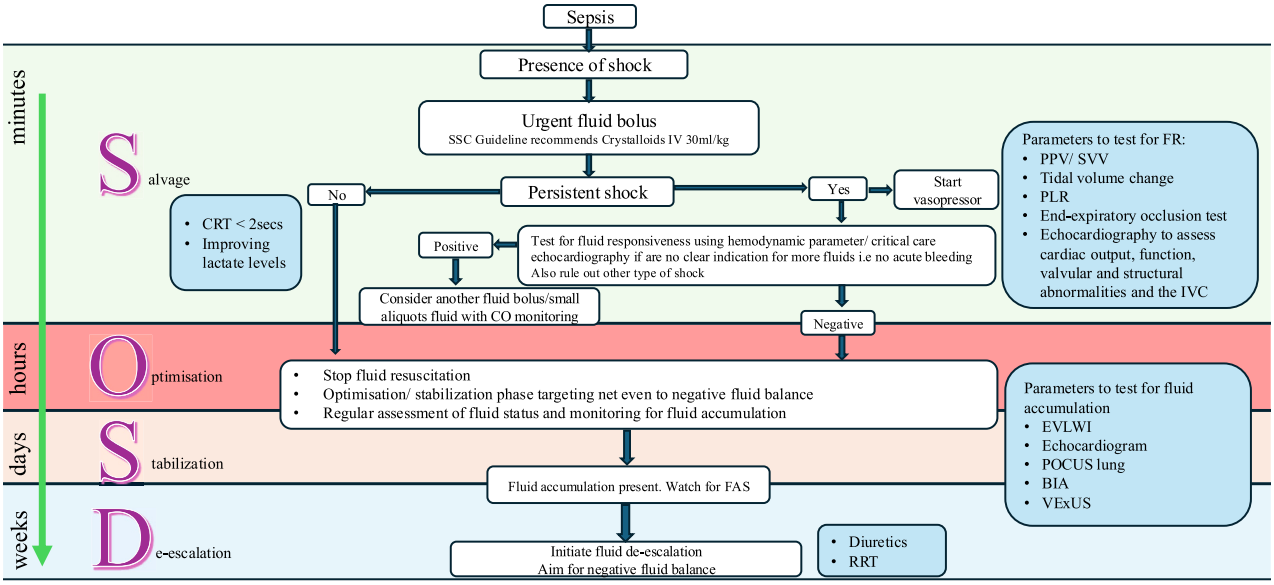

Fig. 2. Algorithm for fluid management strategies in Septic-Associated Acute Kidney Injury, including four phases of fluid resuscitation strategies: Salvage, Optimisation, Stabilisation and De-escalation.
Abbreviations: *BIA,* Bioimpedance analysis; *CO,* cardiac output; *CRT,* Capillary refill time; *EVLWI*, Extravascular lung water index; *FAS,* Fluid accumulation syndrome; *FR*, Fluid responsiveness; *IVC,* inferior vena cavae, *PLR,* passive leg raising test; *POCUS,* Point of care ultrasound; *PPV,* Pulse pressure variation; *RRT,* Renal replacement therapy; *SSC,* surviving sepsis campaign; *SVV,* Stroke Volume variation; *VExUS,* Venous Excess Ultrasound Scoring

3. Fluid management in SA-AKI

In general, fluid management includes several phases. They have been summarised in different models, including the SOSD (salvage, optimisation, stabilisation and de-escalation) concept (Fig. 2), the R.O.S.E. (resuscitation, optimisation, stabilisation, evacuation) framework, and the 4D model [9,10]. The 4D model emphasises that fluids should be regarded as drugs and be prescribed accordingly, including the type of fluid (Drug), volume (Dosing), Duration of treatment and strategy of De-escalation. The rate of fluid delivery is also an important consideration. These conceptual models offer a dynamic framework for clinical practice in the management of AKI in general [9–11]. However, they have not been explicitly studied in patients with SA-AKI.

3.1. Colloids versus crystalloids

Fluid administration commonly involves a choice between two solutions: colloids (e.g. Albumin, gelatins and hydroxyethyl starch (HES)) and crystalloids. These fluids differ in their composition and physiological properties [12]. (Table 1) Colloids are composed of large molecules that are proposed to be more effective in restoring intravascular volume status due to their oncotic property. However, patients with sepsis often have alterations in glycocalyx and increased endothelial permeability, which may lead to extravasation of colloids, abolishing any of these advantages.

3.2. Crystalloids

Crystalloids are aqeuous solutions of mineral salts and other small water-soluble molecules. Saline 0.9 % is the most widely used crystalloid

Table 1
Composition of crystalloid solutions (per 1000 ml) compared to human plasma (adapted from Varrier et al. reference [11]).

Content	Human Plasma	Sodium chloride 0.9 %*	Sodium chloride 0.18 % / 4 % glucose	0.45 % NaCl / 5 % glucose	5 % glucose	Hartmann's solution	Lactated Ringer's	Ringer's acetate	Stereofundin	Plasma-Lyte 148	Normosol™-R
pH	7.35–7.45	4.5–7.0	4.5	3.5–6.5	3.5–5.5	5.0–7.0	6–7.5	6–8	5.1–5.9	7.4	7.4
Na^+ (mmol/l)	135–145	154	31	77	0	131	130	130	145	140	140
Cl^- (mmol/l)	95–105	154	31	77	0	111	109	112	127	98	98
[Na^+]: [Cl^-] ratio	1.28–1.45:1	1:1	1:1	1:1	–	1.18:1	1.19:1	1.16:1	1.14:1	1.43:1	1.43:1
Buffer (mmol/l)	$HC03^-$ 22–28	–	–	–	–	Lactate 29	28 (lactate)	27 (acetate)	Acetate 24/ Malate 5	Acetate 27/ Gluconate 23	Acetate 27/ gluconate 23
K^+ (mmol/l)	4.5–5.0	0	0	0	0	5.4	4.0	4.0	4.0	5.0	5.0
Ca^{2+} (mmol/l)	2.2–2.6	0	0	0	0	2.0	1.4	1	2.5	0	0
Mg^{2+} (mmol/l)	0.8–1.2	0		0		0	0	1.0	1.0	3.0	3.0
Glucose (mmol/l)	3.5–5.5	0	222 (40 g/l)	278 (50 g/l)	278 (50 g/l)	0	0	0	0	0	0
Osmolarity (mOsm/l)	275–295	308	284	406	278	278	273	276	309	294	294

globally. It contains an unphysiological chloride and sodium concentration and no organic buffer. In contrast, buffered solutions (BS) contain lower concentrations of sodium and chloride and additional ions (such as potassium, calcium, and magnesium) and buffers (i.e. bicarbonate, lactate, acetate, or gluconate), achieving electroneutrality. Examples of BS include lactated Ringer's, Hartmann's solution, Plasma-Lyte and Normosol. (Table 1).

Concern about the potential nephrotoxic effects of saline 0.9 % is mainly based on its unphysiological chloride concentration [154 mmol/l], since chloride regulates afferent arteriolar tone, affecting glomerular filtration [13]. However, large randomised controlled trials (RCTs) comparing saline 0.9 % with BS in critically ill patients in general have come to conflicting conclusions. The Saline vs. Plasma-Lyte 148 for ICU Fluid Therapy (SPLIT) trial, conducted across four intensive care units (ICUs) in New Zealand, found no significant difference in AKI or mortality rates among critically ill patients receiving either a BS or saline, though only 4 % of participants were septic [14]. Similarly, the Isotonic Solution Administration Logistical Testing (SALT-ED) trial, a cluster-randomised, multiple cross-over study in non-critically ill patients admitted from the emergency department, showed no significant difference in renal replacement therapy (RRT) administration between patients receiving saline or BS (0.5 % vs. 0.3 %) [15].

The SMART trial, a large cluster-randomised trial involving 15,802 adults across five ICUs in the US demonstrated that BS significantly reduced the composite outcome of death, new RRT initiation, or persistent renal dysfunction compared to saline 0.9 % [16]. A subsequent secondary analysis of patients with sepsis concluded that BS administration was associated with a lower 30-day in-hospital mortality compared with the use of saline 0.9 % [17]. A further ancillary analysis of a subgroup of patients also suggested that BS may modestly reduce AKI biomarkers, indicating a potentially lower risk of AKI with BS [18].

In contrast, the Plasma-Lyte 148 versus Saline Study (PLUS), an RCT evaluating 90-day mortality and renal complications in critically ill adults, including 42.3 % with sepsis, found no significant difference in AKI incidence between both arms [19]. However, the authors compared maximum creatinine level in ICU, maximum increase of serum creatinine and use of RRT as renal outcomes but did not apply the current consensus criteria for AKI. The BaSICS (Effect of Intravenous Fluid Treatment With a Balanced Solution vs 0.9 % Saline Solution on Mortality in Critically Ill Patients) trial was a factorial 2 × 2 RCT in 11,052 patients in 75 ICUs in Brazil, comparing saline 0.9 % with BS [20]. There was no difference in 90-day mortality (26.4 % vs 27.2 %, $p = 0.47$) in the whole cohort, as well as the sepsis subgroup which contributed almost half of the study population. Subgroup analysis revealed increased mortality in patients with traumatic brain injury randomised to BS administration (31.3 % vs 21.1 % $p = 0.02$). An updated meta-analysis including 13 RCTs, comprising 35,884 participants, concluded that the estimated effect of using BS versus saline in critically ill adults ranged from a 9 % relative reduction to a 1 % relative increase in the risk of death and also in the risk of AKI [21]. To date, there have been no RCTs comparing BS with saline 0.9 % specifically in patients with SA-AKI. Furthermore, it remains unknown whether there is a role for other types of crystalloids (ie bicarbonate 1.2 % or 1.4 %) in SA-AKI.

3.3. Colloids

3.3.1. Albumin

A prospective RCT involving 1013 ICU patients in shock found hyper-oncotic albumin (HA) use was associated with an increased risk of ICU mortality and potential renal harm [22]. However, a systematic review of RCTs comparing (HA) with control regimens for volume expansion suggested that HA may reduce resuscitation volume and the incidence of renal impairment [23]. Data also suggest that HA may be beneficial in limiting resuscitation volume compared to hypo- or iso-oncotic albumin. A large RCT comparing isooncotic albumin and saline 0.9 % for fluid resuscitation found that the resuscitation volume ratio between 4 % albumin and saline 0.9 % during the first four days was approximately only 1:1.4, indicating no major volume advantage for albumin [24]. In specific patient populations, albumin use may have a renoprotective role, for instance, in patients with chronic liver disease and sepsis undergoing large-volume paracentesis and in patients with cirrhosis and spontaneous bacterial peritonitis but the role in SA-AKI remains uncertain [25–27]. Further, in patients with traumatic brain injury, the use of albumin has been associated with an increased risk of mortality [28].

3.3.2. HES

The use of HES has been associated with an increased incidence of adverse events, including AKI, need for RRT, coagulopathy, requirement for blood transfusion, and allergic reactions, and is no longer recommended. The Surviving Sepsis Campaign (SSC) and the Food and Drug Administration (FDA) advised against using HES, and the European Commission prohibited its use in critically ill patients. Although not specifically tested, this advice also applies to patients with SA-AKI.

3.3.3. Other colloids

High-quality data on resuscitation with other types of colloids, including gelatine or dextran, are limited [29].

3.4. Phases of fluid management

Early correction of intravascular hypovolaemia and vasoplegia is crucial for patients with septic shock, including patients with SA-AKI. The primary goal is to maintain an adequate cardiac output to ensure organ perfusion. Following the landmark Early Goal-Directed Therapy (EGDT) trial by Rivers et al., many guidelines recommend protocolised fluid resuscitation as guided by central venous oxygen saturation (Scv02), central venous pressure (CVP) and MAP, with administration of at least 30 ml/kg of IV crystalloids during the initial phase of fluid resuscitation in sepsis/septic shock [30,31]. However, subsequent RCTs, including the Australasian Resuscitation in Sepsis Evaluation (ARISE), Protocolized Care for Early Septic Shock (ProCESS), and Protocolized Management in Sepsis (ProMISe), re-investigated this "one size for all" EGDT approach in early septic shock [32–34]. They found no significant mortality benefit and similar RRT requirements between the intervention and control groups. Of note, in all trials, some patients had already received large volumes of fluid before being randomised. The most recent Surviving Sepsis Campaign guideline suggests that for patients with sepsis induced hypoperfusion or septic shock, 30 ml/kg of IV crystalloid fluid should be given within the first 3 h of resuscitation but the evidence was downgraded from previous recommendations [31]. This recommendation also applies to patients with SA-AKI although no trials have been conducted specifically in patients with SA-AKI.

Rate of fluid administration is another important component of fluid resuscitation in general. A retrospective analysis of adult patients admitted to a medical ICU between January 2006 and May 2018 showed that fluid resuscitation at an initial rate of 0.25–0.50 ml/kg/min (ensuring that the recommended 30 ml/kg fluid volume was administered within the first 2 h of septic shock onset) was associated with faster shock reversal and improved survival compared with slower infusion rates [35]. Additionally, a post-hoc analysis of the BaSICs trial evaluated two fluid infusion rates for the fluid challenge (fast, 999 ml/h, versus slow, 333 ml/h) and concluded that a fast infusion rate benefited older patients with sepsis, while a slow rate was preferable for younger, less critically ill patients [36]. However, neither study provided detailed analyses or data on renal-specific outcomes like development of AKI or need for RRT. One retrospective analysis of 597 patients septic shock and AKI showed that those who had received fluid resuscitation at a rate $>$ 0.5 ml/kg/min had significantly higher AKI recovery rates by day 7 (53 %) and day 28 [37]. A faster infusion rate was also associated with improved lactate clearance, reduced need for RRT, and lower mortality. Appropriately powered RCTs are necessary to validate these findings.

Prevention of fluid accumulation has been the focus of several studies. A large RCT comparing conservative fluid management with liberal fluid administration in patients with acute respiratory distress syndrome (ARDS) found no significant difference in 60-day mortality but patients randomised to the conservative arm had a shorter duration of mechanical ventilation and reduced RRT use [38]. A subsequent large RCT comparing restrictive fluid therapy with usual care in ICU patients with septic shock showed no significant difference in 90-day mortality or serious adverse events, including AKI (23.1 % in restrictive group versus 24.5 % in standard group) [39]. A meta-analysis of nine RCTs including 3718 patients focussed on the effects of restrictive fluid resuscitation on severe AKI in patients with septic shock and concluded that a restrictive approach significantly reduced the incidence of severe AKI in patients with septic shock compared to liberal strategies [40]. While no survival benefit was observed, restrictive strategies were also associated with a shorter duration of mechanical ventilation. The review has several limitations, including variability in defining restrictive versus liberal fluid management and AKI reporting that may underestimate severity. Some of the trials that were included also exhibited a moderate risk of bias due to lack of blinding or incomplete outcome reporting, especially for secondary endpoints like RRT.

The Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) trial studied early vasopressor initiation versus liberal fluid initiation after an initial fluid bolus in patients with septic shock [41]. In the restrictive fluid arm, vasopressors were employed to stabilise blood pressure before administering more fluid. The trial was halted for futility after enrolment of 1563 patients. The study revealed no significant difference in mortality or RRT use between the groups, with all-cause 90-day mortality being 14.0 % in the fluid restrictive group versus 14.9 % in the liberal arm. Among 73 patients with end-stage kidney disease, mortality was 27.3 % in those randomised to the restrictive approach compared to 47.5 % in patients in the liberal group (difference: −20.2 %; 95 % confidence interval − 41.9 to 1.5). Of note, the restrictive group received a median of 3.3 l of crystalloids in the first 24 h, casting doubt on the true restrictiveness of the fluid strategy.

The forthcoming results of the ongoing RCT 'Australasian Resuscitation in Sepsis Evaluation: Fluid or vasopressors in emergency department sepsis' (ARISE FLUIDS) investigating volume-first versus vasopressor first strategies are anticipated to provide additional insights into fluid management strategies for septic shock, including patients with SA-AKI. (Clinical Trial.gov Identifier NCT04569942). However, it should be noted that vasopressors differ in how they act on the renal microcirculation and affect glomerular filtration which may confound the interpretation of the results for patients with SA-AKI [42].

3.5. Fluid de-escalation strategies

Congestion is harmful for all organ systems, in particular encapsulated organs like the brain and kidneys. Identifying high risk patients and recognising when to stop fluid administration is crucial to avoid fluid accumulation [43]. The REVERSE AKI trial was a pilot RCT investigating the effects of a restrictive fluid strategy compared to usual care in 100 critically ill patients with AKI who were considered to be euvolaemic at the time of recruitment [44]. 57 % of patients had sepsis. The trial showed a significantly lower cumulative fluid balance at 72 h and day 7 in patients randomised to the fluid restriction approach. Further, significantly less patients in the fluid restriction group were commenced on RRT compared to patients in the usual care group.

Once patients enter the stabilisation phase following fluid resuscitation and are no longer fluid responsive, decongestion and active removal of excess fluid need to be considered [10,45,46]. The most common strategies to remove excess fluid include diuretics (single or combination therapy) and/or RRT.

Mechanical fluid removal with ultrafiltration may be indicated in case of pharmacologic failure or development of serious adverse events with diuretic therapy [47,48]. It can be performed intermittently or continuously. Slow, sustained fluid removal is preferred in hemodynamically unstable patients to allow vascular refilling and to prevent hemodynamic instability [47]. Both, inadequate fluid removal resulting in prolonged fluid overload, and excessive fluid removal causing haemodynamic instability are detrimental to renal recovery and patient outcomes [49,50]. Retrospective analysis of 820 critically ill patients treated with RRT of whom 39 % had sepsis showed that successful fluid removal was associated with better outcomes [49]. Hemodynamic instability during RRT, often manifested as intradialytic hypotension (IDH), can compromise renal blood flow, reduce glomerular filtration, contribute to tubular injury and delay renal recovery [50]. In one study, the incidence of hypotension within the first hour of RRT initiation was 43 % [51]. Whether the risk of IDH in patients with SA-AKI is different compared to patients with other types of AKI is unknown.

IDH limits adequate fluid removal but may also negatively affect renal recovery. Strategies exist to reduce the risk of IDH [50,52,53]. In a RCT, Macedo et al. demonstrated that intravenous albumin significantly reduced the occurrence of IDH and achieved better fluid removal in hospitalised patients with hypoalbuminaemia undergoing RRT [52].

Table 2
Parameters in assessing preload responsiveness and volume tolerance.

Method	Interpretation	Advantages	Limitations
PLR			
• PLR to 45° in recumbent patients produces hemodynamic changes that mimic volume expansion • PLR mobilizes approximately 300 ml blood from lower extremities and transiently increase venous return	Increase in CO by >10 % in preload-dependent states within 1 min may predict fluid responsiveness	• High specificity and sensitivity in predicting • Validated regardless of type of ventilation, cardiac rhythm, tidal volume and lung compliance • Can be used in non-ventilated patients	• False negative if using venous compression stockings or intra abdominal pressure ≥ 16 mmHg • Cannot be used in neurotrauma • May cause discomfort in awake patients
Pulse Contour analysis			
• PPV • SVV Plethysmography variability index • Modified pulse oximeter to measure respiratory cycle-induced variation in the plethysmograph waveform	CO > 15 % predictive of preload responsiveness	• Dynamic challenge without the need for fluid infusion • Utilizes current arterial access without need for further invasive procedure	Requires frequent calibration. Unreliable in: • Spontaneously breathing patients • Low tidal volume < 8 ml/kg • Reduced lung compliance • Cardiac arrhythmias • High intra-abdominal pressure • Open thorax • Low heart rate /Respiratory rate ratio < 3.6 (severe bradycardia or high frequency ventilation) • False positive in right ventricular dysfunction
End-expiratory occlusion test Ventilator is temporarily stopped in end-expiration for 15–30s and 500mls saline is infused	Increase in CO ≥ 5 % predicts preload responsiveness	• Can be used in low tidal volume ventilation	• Limited to intubated patients
Mini fluid challenge (100–200 ml) • Using the same principle as PLR	Increase in CO > 15 % predicts preload responsiveness	As an alternative in patients with low tidal volume	• Need precise technique for cardiac output monitoring (SVV or PPV) • Short lived effect, may risk to fluid accumulation in repeated mini bolus
TV challenge			
• Transiently increase TV from 6 ml/kg to 8 ml/kg for one minute and record the changes of PPV	Change in PPV predicts preload responsiveness Reading >3.5 % predicts fluid responsiveness	Can be used in TV 6 to 8 ml/kg	Unreliable in: • Spontaneously breathing patients • Cardiac arrhythmias • High intra-abdominal pressure • Open thorax
Echocardiography			
Respiratory variations of LVOT VTI using pulse wave doppler	• Normal VTI 18-22 cm • For VTI < 18 cm, an increase >10 % upon fluid bolus or PLR predicts preload responsiveness	• Non invasive • Reliable in spontaneously breathing or invasive mechanical ventilation	• Needs trained personnel for good image acquisition • Patient needs to be in sinus rhythm
Pulsed wave doppler and tissue doppler imaging for left ventricular filling pressure	High filling pressures indicated by E/A > 1.8 and/or E/E' > 15 • "kissing' LV with low end-diastolic area (<5cm²/m²) may suggest in a non-hypertrophied ventricle may indicate severe preload reduction	• Useful when continuous cardiac monitoring is not available • Non-invasive • Reliable in spontaneously breathing or invasive mechanical ventilation • Transthoracic echocardiography is non-invasive	• Reliable in patient on invasive mechanical ventilation, without spontaneous effort • Tidal volume 6-8 ml/kg (false negative in very low tidal volume) • False positive result in unresponsive patient with severe right ventricular dilatation • Need for trained personnel
Cardiac chamber	• Caution on volume resuscitation when RV is severely dilated with impaired function **In a mechanically ventilated patients with no spontaneous breathing efforts:** Distensibility index = (IVCmax- -IVCmin)/ IVCmin X 100 % Value >18 % predicts volume responders	• Reliable in spontaneously breathing or invasive mechanical ventilation	• A restrictive mitral inflow is seen in young patients • Need for trained personnel • Operator dependent • A negative scan does not exclude fluid responsiveness • Affected by changes in intra-thoracic pressure/ high intra-abdominal pressure (high PEEP may cause IVC distension) • Poor window in obese patients • Caution with fluids when diameter > 25 mm (look at PEEP and other parameters of right heart failure and cardiac output)
IVC assessment	**In spontaneously breathing patients:**		

(*continued on next page*)

Table 2 (*continued*)

Method	Interpretation	Advantages	Limitations
	IVC Collapsibility index = (IVCmax-IVCmin)/ IVCmax X 100 % Value >42 % predicts volume responsiveness		
EVLWI • A marker of pulmonary edema, vascular permeability and ARDS	Transpulmonary thermodilution • A high value ≥12 % quantifies pulmonary edema	Use during resuscitation guide towards fluid restriction and removal strategy	• Does not differentiate cause of lung congestion i.e. cardiogenic versus non-cardiogenic pulmonary edema • Complicated measurement technique • Invasive • Over-estimation occurs in high PEEP and in lung resection • Under-estimation in pulmonary vascular occlusion
POCUS Lung	B profiles suggest fluid accumulation in lungs Pleural effusions	• Non-invasive, easy to perform	• Operator dependent • Non-specific may suggest other pathology i.e. infective causes
BIA Constant electrical current stimulation for identification of thoracic or body impedance variations induced by vascular blood flow	Identify excess body water / dry weight	• Non-invasive	• Inconsistent outcomes in case reports
VExUS score Grading of organ venous congestion (liver and kidney) pulsatility index guide decision on when to stop fluid and when to remove fluid	Interpretation is by grading system. **Grade 0 (No congestion)** • IVC < 2 cm **Grade 1 (Mild congestion)** • IVC ≥ 2 cm and any combo of normal or mildly abnormal patterns in hepatic/ portal/ renal doppler **Grade 2 (Moderate congestion)** • IVC ≥ 2 cm and ONE severely abnormal pattern from either hepatic/ portal or renal doppler **Grade 3 (Severe congestion)** • IVC ≥ 2 cm and ≥ 2 severely abnormal pattern	• Allows identification of organ venous congestion through a bedside noninvasive technique • Indicates when to stop fluid and when to remove fluid • Prompt identification of causes of venous congestion i.e. right heart failure	• Operator dependent • Skilled physician in ultrasound • Need *Pulse Wave Doppler* function in Ultrasound machine (some handheld ultrasound may be devoid of this function) • May have false positive or higher grade in cirrhosis

Abbreviations: PLR, Passive leg raising; CO, cardiac output; E/A, early to late ventricular filling velocity; E/e'. index to evaluate the LV filling pressure; LV, left ventricle; IVC, inferior vena cavae; IAP, intra abdominal pressure; VR, venous return; FR, fluid responsiveness; VExUS, Venous Excess Ultrasound Score; VTI, velocity time integral; PEEP, positive end-expiratory pressure; ARDS, acute respiratory distress syndrome; TV, tidal volume.

However, a consensus guideline from the International Collaboration for Transfusion Medicine suggested not to use albumin for fluid removal or prevention of intradialytic hypotension in patients undergoing RRT based on lack of data confirming cost-effectiveness [54].

3.6. Monitoring during fluid management

Lactate is one of the most commonly used markers of hypoperfusion and resuscitation endpoint. Rapid lactate reduction in retrospective studies correlates with better outcomes [55]. Although most recent trials question the benefit of strict goal-directed resuscitation protocols, continuous lactate monitoring remains useful during the initial hours of resuscitation [56]. Capillary refill time (CRT) has proven to be equally effective as lactate in guiding resuscitation in septic shock, which is particularly important for settings where routine monitoring of lactate concentrations may not be available [57]. Other tools to guide fluid resuscitation include haemodynamic parameters such as pulse pressure variation (PPV), stroke volume variation (SVV), passive leg raising (PLR) and echocardiography [58]. Table 2 summarises different methods for evaluating fluid responsiveness.

Monitoring of volume status during fluid removal can be challenging. Clinical indicators such as oedema, body weight, low haematocrit, cumulative fluid balance, pulmonary congestion on x-ray and reduced $Pa0_2/Fi0_2$ ratio are imprecise parameters of volume status. Invasive hemodynamic monitoring provides more precise information. For instance, transpulmonary thermodilution techniques allow indirect transpulmonary measurement of extravascular lung water index (ELVWI) [59,60].

Non-invasive techniques like point-of-care ultrasound (POCUS) are increasingly used to evaluate fluid accumulation. POCUS, particularly lung ultrasound, is more sensitive than chest radiographs in detecting pleural effusions [61]. The Venous Excess Ultrasound (VExUS) scoring system is an emerging tool with studies suggesting a correlation between venous congestion and higher mortality rates [62,63]. Combined with lung ultrasound, VExUS may guide fluid de-escalation strategies. The role of N-terminal pro-brain natriuretic peptide (NTPro-BNP), a biomarker of increased atrial filling pressure, to guide fluid removal is uncertain [64].

A study in patients recovering from acute circulatory failure who required fluid removal with RRT found that a positive PLR test before fluid removal predicted IDH and hemodynamic intolerance [65]. Accordingly, PLR testing can be useful to identify patients at higher risk of haemodynamic instability during fluid removal.

4. Confounding factors

There are 711.9/100,000 people living with heart failure globally. Further, there is a reported prevalence of de novo septic cardiomyopathy of 20 % in published datasets on sepsis-induced cardiomyopathies [66,67]. This significant cohort introduces the complexity of a mixed cardiogenic and distributive shock state that requires further physiological understanding of the Frank-Starling mechanism and knowledge of potential structural and valvular defects within the heart. (Fig. 2) Excess fluid can be particularly detrimental through over-distension of the cardiac chambers, leading to venous congestion and renal impairment. The use of vasodilators to manage cardiogenic shock can compound a septic vasodilatory state and, thus, arterial perfusion pressure of the kidneys. Therefore, in case of existing or suspected cardiac dysfunction, the key is sufficient cardiac output monitoring through echocardiography or invasive monitoring devices such as pulmonary artery catheter to guide appropriate vasoactive and fluid management.

5. Future direction and research gaps

Following the completion of more than 13 RCTs and inclusion of more than 35,000 patients, it is unlikely that more large-scale RCTs comparing BS versus saline 0.9 % will be conducted in critically ill patients in general. To date, fluid management has not been specifically studied in patients with SA-AKI and all recommendations are extrapolated from studies in critically ill patients in general. Furthermore, it is unknown whether there is a role for bicarbonate or other types of crystalloids in SA-AKI. The development of novel fluid compositions that might mitigate the risks of AKI, such as solutions optimised for electrolyte balance or anti-inflammatory properties, should also be considered.

In addition, better tools are needed to identify the time point when an adequate fluid status has been restored and fluid administration should cease to prevent fluid overload [68]. In fact, the need for strategies to individualise fluid resuscitation in patients with sepsis was identified as one of 5 top priorities for future research [69].

The role of mixed cardiogenic and distributive shock in SA-AKI complicates fluid therapy. Understanding the interplay between fluid therapy and impact on cardiac output in this subset remains a critical gap in knowledge and addressing these gaps will help refining fluid management strategies for AKI and may improve both short-term and long-term outcomes in critically ill patients.

6. Conclusions

Effective fluid management is crucial in the treatment of SA-AKI but has not been explicitly studied. While early aggressive fluid resuscitation may be vital, the subsequent phases require careful balance to avoid fluid accumulation and venous congestion which can exacerbate AKI. Crystalloids are recommended for management with a preference for BS over saline 0.9 %. There are a range of haemodynamic measures that can be deployed to assess fluid status as well as pharmacological and mechanical mechanisms to remove excess fluid. Ultimately, fluid management in SA-AKI must be individualised, with close monitoring to adapt treatment strategies across the different phases of care.

CRediT authorship contribution statement

Nurul Zaynah Nordin: Methodology, Writing – original draft. **Waqas Akhtar:** Methodology, Writing – review & editing. **Marlies Ostermann:** Supervision, Conceptualization, Writing – review & editing, Methodology.

Consent for publication

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Declaration of competing interest

The authors declare no conflict of interest.

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